# Ambrisentan (BSF 208075) Test Phase Chronology (IND 63,412 and IND 64,915)

| | Date | Document Type | Document Title | Discussed Matter |
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| 1 | 10/10/2001 | FDA submission – IND | Initial submission – IND on BSF 208075 for Chronic Renal Failure | |
| 2 | 11/02/2001 | FDA correspondence – Phone call | FDA Contact Report – Clinical Hold | N/A |
| 3 | 11/09/2001 | FDA correspondence – Phone call | FDA Contact Report – To discuss IND and the reasons it is being placed on Clinical Hold | "a) the potential of BSF 208075 to cause testicular tubular atrophy in humans…" "b) the potential of BSF 208075 to cause liver toxicity in humans…" |
| 4 | 11/13/2001 | FDA correspondence – Letter | IND Clinical Hold letter for BSF 208075 | "The Agency is particularly concerned about the state of knowledge regarding testicular effects." |
| 5 | 11/14/2001 | FDA correspondence – Phone call | FDA Contact Report – To ask about a potential IND for BSF 208075 for an indication of Pulmonary Arterial Hypertension | "I called and asked Zelda about an IND for BSF 208075 for Pulmonary Arterial Hypertension. I asked if an entirely new IND would need to be submitted…" "She said it may be possible to use the same IND… she said she had checked with her supervisor and the supervisor said to submit another IND for Pulmonary Hypertension." |
| 6 | 11/19/2001 | FDA correspondence – Phone call | FDA Contact Report – To ask about the letter received from the Division and see when to expect the Clinical Hold letter | "I then asked when to expect the IND Clinical Hold letter for BSF 208075. She said the letter was supposed to go out on November 9th, but they had computer problems so it was not signed until November 13th." |
| 7 | 12/07/2001 | FDA correspondence – Phone call | FDA Contact Report – To ask when the FDA minutes from the November 9th teleconference would be available and to ask about the | "I called and asked Zelda when the minutes from the November 9th teleconference regarding the clinical hold on BSF 208075 would be available." "I called Zelda back and asked about the mention in the clinical hold letter of hypertension rather than |

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| | | | mention of "hypertension" as the target indication in the clinical hold letter | renal failure as the target indication." |
| 8 | 12/12/2001 | FDA correspondence – Fax | Minutes of 11/9/01 Telecon from FDA | "Dr. Lipicky said the same toxicology problem with the testes exits no matter what the indication." |
| 9 | 12/14/2001 | FDA correspondence – Phone call | FDA Contact Report – To revise the clinical hold letter and to confirm that Dr. Lipicky had referred to the Advisory Committee meeting scheduled for 1/17/01. | "Zelda also said that they would revise the clinical hold letter for BSF 208075 to take out the inadvertent use of the word hypertension as the target indication." |
| 10 | 12/18/2001 | FDA correspondence – Letter | Revised IND Clinical Hold letter for BSF 208075 (the November 13, 2001 letter is superseded by this version.) | |
| 11 | 12/20/2001 | FDA correspondence – Fax | Type A meeting request | "BSF 208075 is currently in development for potential treatment of chronic renal failure (CRF) and primary arterial hypertension (PAH)" "Objectives/outcomes expected from the meeting: … To discuss a clinical development plan for the treatment of patients with PAH, that includes women only in the initial dose-ranging study and uses 6-minute walk as the primary efficacy endpoint." |
| 12 | 1/16/2002 | FDA correspondence | FDA Contact Report – To discuss the Agency's preclinical concerns, a different dose-ranging study for CRF, the overall clinical development strategy including an indication of PAH and confirm that the plan for a Clinical Hold Complete | "GENERAL COMMENTS… The Agency said BSF 208075 is not the average drug candidate and they would put special requirements on it for approval. They said the drug must prove itself to be unequivocally valuable and should ideally distinguish itself from bosentan, i.e., prove to be more safe, more efficacious, or expand the PAH patient population in which efficacy and safety are demonstrated." |

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| | | | Response is acceptable. | "6. Would the BSF 208075 clinical development program for treatment of patients with PAH, consisting of the proposed Phase II study in women (see Attachment 3) and a single Phase III study in men and women, fulfill regulatory requirements for an NDA submission? RESPONSE: The Agency said that generally they would require similar data to what was submitted for bosentan, i.e., that generated from two trials using the 6-minute walk test." |
| 13 | 1/25/2002 | FDA correspondence – Phone call | FDA Contact Report – To discuss the toxicology follow-up study and determination of the therapeutic index in rats | "Myogen is most interested in this relative to the two indications they are considering: Chronic Renal Failure (CRF) and Pulmonary Arterial Hypertension (PAH). For PAH, Myogen is considering a microcrotaline model, using several different doses, with dosing to steady state." |
| 14 | 4/12/2002 | FDA submission – IND | IND 63,412, Serial #004 – Request for Protocol Review and Comment (PAH) | "This submission is in response to a recommendation received from the Agency at a meeting with Myogen for IND 63,412 that was held on January 16, 2002. During that meeting a proposal to also investigate the use of BSF 208075 in patients with Pulmonary Arterial Hypertension (PAH) was discussed."<br>"Myogen understands that a separate BSF 208075 IND for the indication of PAH will be required and plans to submit the separate IND as soon as possible, upon receipt of your comments regarding the acceptability of the proposed protocol." |
| 15 | 4/12/2002 | FDA correspondence – Phone call | FDA Contact Report – To confirm that the Clinical Hold complete Response had been received at FDA | "I stated that I was submitting it to the existing IND for Chronic Renal Failure, but understood that a different IND would eventually be needed." |
| 16 | 5/02/2002 | FDA correspondence – Phone call | FDA Contact Report – To confirm that Amendment | "I called Zelda and left a message asking her to let me know if she received the submission with the |

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| | | | to the Complete Response to Clinical Hold had been received at FDA and to ask about having a meeting with the Division on May 9, 2002 to discuss the Protocol for PAH. | Amendment to the Complete Response to Clinical Hold. I also asked her if she thought the Division would be willing to meet with use after the Clinical Hold Review Committee Meeting on May 9th to discuss the Protocol Review Request for Pulmonary Arterial Hypertension (PAH)." |
| 17 | 5/03/2002 | FDA correspondence – Phone call | FDA Contact Report – To inform me that the Clinical Hold for IND 63,412 was officially lifted and to offer a teleconference to discuss the protocol for Pulmonary Arterial Hypertension. | "I said that the documents (PAH Protocol, Informed Consent and Investigator's Brochure) were previously submitted but that we would make the same changes to the PAH protocol and informed consent form that had been made earlier this week to the Renal Failure documents and submit them again." |
| 18 | 5/03/2002 | FDA correspondence – Letter | FDA letter lifting clinical hold | "We have completed the review of your submission, and have concluded that clinical trial (AMB-201) may be initiated." |
| 19 | 6/03/2002 | FDA correspondence – Phone call | FDA Contact Report – To inform Zelda that the BSF 208075 IND for Pulmonary Arterial Hypertension was shipped to FDA on June 3, 2002. | |
| 20 | 6/03/2002 | FDA correspondence – Phone call | FDA Contact Report – To check on and confirm the receipt on the IND submission | "I further explained that based on her recommendation in a previous phone contact, all of the preclinical study reports were reprinted in this IND, and not cross-referenced to the reports in the BSF 208075 IND for Chronic Renal Failure (IND 63,412) in order to increase the ease of review." |

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